67. (Amended) The method of claim 60 wherein said anti-CD40L antibody is a humanized, primatized, or chimeric anti-CD40L antibody.

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68. (Amended) The method of claim 67 wherein said anti-CD40L antibody is humanized MAb 89-76 or humanized MAb 24-31.

69. (Amended) The method of claim 60 wherein said anti-CD20 antibody is radiolabeled with ^{90}Y.

71. (Amended) The method of claim 60, which further comprises administering at least one alkylating chemotherapeutic agent.

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72. (Amended) The method of claim 71 wherein said alkylating chemotherapeutic agent is selected from the group consisting of cyclophosphamide, chlorambicil, procarbazine, and lomustine.

82. (Amended) The method of claim 80 wherein the anti-CD20 antibody is IDEC-C2B8 and the anti-CD40L antibody is humanized MAb 24-31.

83. (Amended) The method of claim 81 wherein the anti-CD20 antibody is

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IDEC-C2B8 and the anti-CD40L antibody is humanized MAb 24-31.

84. (Amended) The method of claim 80 which further comprises administering at last one alkylating chemotherapeutic agent.

85. (Amended) The method of claim 81 which further comprises administering at last one alkylating chemotherapeutic agent. --

Claims 80 and 81 are unchanged:

80. The method of claim 60 wherein the anti-CD20 antibody is administered prior to the anti-CD40L antibody.

81. The method of claim 60 wherein the anti-CD20 antibody is administered after the anti-CD40L antibody.

Claims 86-97 are new claims:

-- 86. The method of claim 66 wherein said anti-CD20 antibody is IDEC-C2B8.

87. The method of claim 86 wherein said anti-CD40L antibody is humanized MAb 24-31.

88. The method of claim 68 wherein said anti-CD40L antibody is humanized MAb 24-31.

89. The method of claim 60, wherein a weekly dose of said anti-CD20 antibody is 0.4 to 20 mg/kg body weight, and a dose of said anti-CD40L antibody is 0.5 to 10 mg/kg body weight.

C5

90. The method of claim 69 wherein said anti-CD20 antibody that is radiolabeled with ^{90}Y is a non-chimeric murine antibody.

91. The method of claim 84 wherein said alkylating chemotherapeutic agent is selected from the group consisting of cyclophosphamide, chlorambicil, procarbazine, and lomustine.

92. The method of claim 85 wherein said alkylating chemotherapeutic agent is selected from the group consisting of cyclophosphamide, chlorambicil, procarbazine, and lomustine.

93. A method for treating a B cell leukemia comprising administering a therapeutically effective amount of:

(i) IDEC-C2B8, and

(ii) humanized MAb 24-31.

94. The method of claim 93 wherein IDEC-C2B8 is administered prior to humanized MAb 24-31.

95. The method of claim 93, wherein a weekly dose of said IDEC-C2B8 is 0.4 to 20 mg/kg body weight, and a dose of said humanized MAb 24-31 is 0.5 to 10 mg/kg body weight.

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96. The method of claim 93 wherein said B cell leukemia is selected from the group consisting of chronic B cell leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, and Burkitt's type leukemia.

97. The method of claim 93 wherein IDEC-C2B8 is radiolabeled with ^{90}Y.

98. The method of claim 93 which further comprises administering at least one alkylating chemotherapeutic agent.

99. The method of claim 98 wherein said alkylating chemotherapeutic agent is selected from the group consisting of cyclophosphamide, chlorambicil, procarbazine, and lomustine. --

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Support in the Specification for the Amendments and Added Claims:

Support for limiting claim 60 to a method comprising administering an anti-CD20 antibody having B-cell depleting activity, or a fragment thereof having such activity, is found in the specification, for example, at page 3, lines 16-19, which describes activities of an anti-CD20 antibody as including killing human lymphocytes in vitro and depleting normal B cells of a primate (macaque) in vivo.

Support for limiting claim 60 to a method comprising administering an anti-CD40L antibody that antagonizes interaction of CD40 and CD40L, or a fragment thereof having such activity, is found in the specification, for example, at page 8, lines 9-10, which describes activities of an anti-CD40L antibody as including antagonizing CD40-CD40L interactions; and also in original claim 22.

Support for limiting claim 67 and 68 to a method comprising administering an anti-CD20 or anti-CD40L antibody, respectively, that is a humanized, primatized, or chimeric

antibody, is found in the specification, for example, at page 10, lines 18-19, and page 11, lines 1-2.

Support for replacing the trademarked term Rituxan® with IDEC-C2B8, e.g., in claims 82, 83, and 86, is found in the specification, for example, at page 3, line 7.

Support for reciting an anti-CD40L antibody that is humanized MAb 89-76 or humanized MAb 24-31 in claim 68 is found in the specification, for example, at page 17, lines 8-19. Additional support is found in the description of using of IDEC-131, which is a humanized MAb 24-31 antibody, as described in U.S. Application No. 08/554,840 (issued as U.S. Patent No. 6,001,358), which is incorporated by reference into the present application in its entirely (p. 16, lines 3-5).

Support for reciting the alkylating chemotherapeutic agents listed in claim 72, is found in the specification, for example, at page 39, lines 7-21.

Support for administering a weekly dose of said anti-CD20 antibody of 0.4 to 20 mg/kg body weight as recited in claim 89 is found in the specification, for example, at page 42, lines 3-8. Support for administering a dose of said anti-CD40L antibody of 0.5 to 10 mg/kg body weight as recited in claim 89 is found in the specification, for example, at page 27, lines 4-7.

Support for using a non-chimeric murine anti-CD20 antibody that is radiolabeled with ^{90}Y antibody as recited in claim 90 is found in the specification, for example, at page 43, lines 15-19.

Regarding the objections to claims 68 and 69:

Claims 68 and 69 are amended to correct the typographical errors identified by the examiner, and spelling of the recited chemotherapeutic agents has been reviewed as advised by the examiner.

Regarding the rejection of the claims under 35 U.S.C. § 112, 2nd paragraph:

Claims 66 and 68 were rejected under 35 U.S.C. § 112, 2nd paragraph, as being indefinite, because the term "Rituxan®" recited in claim 66 is a trademark, and the characteristics of "IDEC-131" recited in claim 68 are not clearly described in the specification.

Claim 66 is amended by deleting the trademark "Rituxan®;" and the antibody identified as "Rituxan®" in the specification is referred to in the amended and new claims by

the non-trademark, technical designation "IDEC-C2B8," support for which is found in the specification, for example, at page 3, line 7, as stated above.

Claims 68 is amended by deleting the term "I?DEC-131," and the antibody identified as "IDEC-131" in the specification is referred to in the amended and new claims as humanized MAb 24-31, support for which is found in the specification, for example, at page 17, lines 8-19, as stated above. That IDEC-131 is humanized MAb 24-31 is described in U.S. Application No. 08/554,840 (now U.S. Patent No. 6,001,358), which is incorporated by reference into the present application in its entirely, stated above.

Regarding the rejection of the claims under 35 U.S.C. § 103(a):

Claims 60-85 were rejected under 35 USC §103(a) as being as obvious in view of Kaminski et al. and/or Anderson et al., in view of Smiers et al., Schattner et al., Gruss et al., Renard et al., Black et al., and Noelle et al., and in view of standard chemotherapeutic treatments. This rejection is respectfully traversed.

Both Kaminsky et al. and Anderson et al. teach that CD20 antigen is present on normal and malignant B cells, and that anti-CD20 antibodies may be cytotoxic to neoplastic B cells; however, neither reference suggests administering both anti-CD20 and anti-CD40L antibodies in combination to treat leukemia.

Kaminsky et al. (U.S. Patent No. 6,287,537, Radioimmunotherapy of Lymphoma Using Anti-CD20 Antibodies) describes the presence of CD20 antigen on normal and malignant B cells, including B cell leukemias, and states that anti-CD20 antibodies have been used in ex vivo purging of bone marrow prior to autologous bone marrow transplantation in patients with refractory leukemia and lymphoma; however, Kaminsky et al. teach that, "[b]ecause of the limited efficacy of unmodifioed antibodies in general, recent attention has focused on the use of antibodies conjugated to cytotoxic agents," and that "radioisotopes are especially attractive, as lymphomas are especially sensitive to the effects of radiation." See column 2. As the name of the patent implies, the focus of Kaminsky et al. is on describing methods for radiolabeling anti-CD20 antibodies, and using the radiolabeled anti-CD20 antibodies for radioimmunotherapy of lymphoma. Accordingly, one of ordinary skill in the art would reasonably view Kaminsky et al. as teaching away from using non-radiolabeled anti-CD20 antibodies to treat B cell malignancies.

The primary focus of Anderson et al. (U.S. Patent No. 5,843,439, "Therapeutic Application of Chimeric and Radiolabeled Antibodies to Human B Lymphocyte Restricted

Differentiation Antigen for Treatment of B Cell Lymphoma") is also treatment of B cell lymphoma. Anderson et al. describes radiolabeling non-chimeric murine 2B8 anti-CD20 antibodies with ^{111}In and ^{90}Y and using the radiolabeled anti-CD20 antibodies to localize lymphoma cells in vivo; making chimeric C2B8 anti-CD20 antibodies and using these to lyse human B cells in vitro, and to deplete B cells in macaques; and administering C2B8 and ^{90}Y-labeled 2B8 anti-CD20 antibodies in combination therapy to treat lymphoma in an animal model. Anderson et al. do not disclose or suggest treating leukemia by administering anti-CD20 in combination with anti-CD40L antibodies.

As discussed in the response to the previous office action, Smiers et al., Schattner et al., Gruss et al., and Renard et al., are cited as teaching that at the time the invention was made, it was known that many B cell leukemias expressed both CD40 and CD20 antigens. Significantly, these references teach that for normal B lymphocyte, the binding of CD20 to its ligand stimulates the B cells to leave G0 and enter G1 of the cell cycle, and the binding of CD40 to its ligand stimulates the B cells to begin DNA synthesis and undergo mitosis, and co-activation of both CD20 and CD40 results in a full mitogenic response of normal B cells (Smiers et al., p. 125). However, as the cited references show, leukemia cells show aberrant responses to CD20 and CD40 ligands. For example, Schattner et al. teaches that CLL cells express surface CD40 and are activated by CD40 ligation, and that a subset of CLL cells also express surface CD40L that might function in a paracrine fashion, as evidenced by their ability to induce normal B cells to produce IgG. Smiers et al. show that ALL cells often fail to respond either to CD20 ligand or to CD40 ligand, as if the requirement for the signal is bypassed (see Tables I and II, p. 127, and discussion on page 129). Only 5 of 35 ALL cell samples showed an additive response to the combination of CD20 ligand and CD40 ligand (Table III. P. 129). Gruss et al. teaches that CD40 is generally present on B lineage CLL and ALL cells; but that only about 50% of B lineage ALLs show a proliferative response to CD40L expressed on the surface of activated CD4+ T cells (pp. 403-404). Renard et al. similarly reports that about 50% (4/9) leukemic B cell precursor blasts from patients with ALL could be stimulated to proliferate by activated CD4+ T cells bearing CD40L surface antigens, and that only one sample of leukemic B cell precursors out of seven that had detectable CD40 responded in a CD40-dependent fashion (p. 5167). Two ALL leukemic B cell precursor samples bearing the same early pre-B phenotype (CD10+, CD34+, CD40+, cμ) responded differently to the activated CD4+ T cells bearing CD40L surface antigens (paragraph bridging pp. 5167-5168).

Taken as a whole, the teachings of Smiers et al., Schattner et al., Gruss et al., and Renard et al., show that leukemia cells show considerable heterogeneity, both in their surface antigen profiles, and in the responses to ligation of surface antigens. Gruss et al. disclosed using an anti-CD40L antibody conjugated to a cytotoxic protein to inhibit growth of neoplastic precursors in B-lineage ALL and NHL samples; however, nothing in the Smiers et al., Schattner et al., Gruss et al., or Renard et al. references discloses or suggests the combined use of an anti-CD40L antibody and an anti-CD20 antibody to treat a B cell leukemia. The claimed invention includes the use of unconjugated and non-radiolabeled anti-CD40L and anti-CD20 antibodies. At the time the application was filed, it was unknown whether the combination of these two unconjugated and non-radiolabeled antibodies would effectively inhibit growth or kill leukemic cells.

Figure 3a is a histogram showing % Cytoxicity resulting from incubating IDEC-131 (humanized MAb 24-31) anti-CD40L antibodies with primary CLL cells cultured in the absence (four bars on left side of figure) and in the presence (four bars on right side of figure) of 5 μg/ml soluble CD40L (gp39). This concentration of sCD40L is comparable to the levels of biologically active sCD40L present in the serum of patients with CLL (see Younes et al., Brit. J. Haematol., 1998, 100(1):135-141, abstract attached). As shown in Table II (p. 53), primary CLL cells cultured in vitro undergo apoptotic cell death, but their viability is extended by culturing them in medium containing 5 μg/ml sCD40L. Fig. 3a shows that CLL cells exposed to levels of sCD40L similar to those present in the serum of patients with CLL are sensitized to the cytotoxic effects of unconjugated IDEC-131 antibodies. Gruss et al. noted that blocking CD40-CD40L interactions induce apoptosis in some lymphoma cell lines (p. 405, left column), however, this teaching would not have led persons of ordinary skill in the art to reasonably expect that blocking CD40 ligation with anti-CD40L antibodies would be cytotoxic to leukemia cells, and would have amounted only to an invitation to try. Black et al. and Noelle et al. also fail to cure the defects of the primary references.

Fig. 3b shows that CLL cells exposed to levels of sCD40L similar to those present in the serum of patients with CLL are also sensitized to cytotoxic effects of unconjugated IDEC-C2B8 antibodies. This result clearly depends on the metabolic responses of the CLL cells to binding by the anti-CD20 antibodies, and could not have been predicted by persons of ordinary skill in the art with a reasonable expectation of success. The ability of non-radiolabeled, unconjugated B cell-depleting anti-CD20 antibodies to induce cell death of leukemia cells in vivo has only recently come to be appreciated by persons in the art, with the

reporting of the results of clinical trials and mechanistic studies. For example, Tallman et al. report that IDEC-C2B8 antibodies are effective in treating CLL (Semin Hematol., 2002, 39(4 Suppl 3):12-9, abstract attached). Byrd et al. report that non-radiolabeled, unconjugated IDEC-C2B8 antibodies clear CLL cells from patients by a mechanism involving caspase activation and induction of apoptosis (Blood, 2002, 99(3):1038-43, abstract attached); and Pedersen et al. report that the IDEC-C2B8 antibodies induce apoptosis in B cell CLL cells through a signaling pathway dependent on P38 MAP-kinase activation (Blood, 2002, 99(4):1314-9, abstract attached).

The cited references do not provide one of ordinary skill in the art with a reasonable expectation that non-radiolabeled, unconjugated anti-CD20 antibodies or anti-CD40L antibodies, acting alone or in combination, will successfully inhibit growth of leukemia cells. Rather, they provide a suggestion to try and see what happens. "Obvious to try" is not the standard for supporting an obviousness rejection under 35 USC 103. See In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988).

By the same token, the cited references do not disclose or suggest administering an anti-CD40L antibody and an anti-CD20 antibody in combination to treat a B cell leukemia. Under U.S. Patent Law, a suggestion or motivation to combine various teachings of prior art references to obtain the claimed invention, and a reasonable expectation that the combination will operate successfully, must be found in the prior art, not in applicant's disclosure. See M.P.E.P. § 2143, Basic Requirement of a *Prima Facie* Case of Obviousness, citing In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The cytotoxic effects of the two antibodies on B cell leukemia cells sensitized by sCD40L, as described in the disclosed example, could not have been predicted by persons of ordinary skill in the art. As pointed out in the response to the last Office Action, combination therapies were routinely used in treating malignancy at the time the application was filed; however, they generally involved the combined use of radiotherapy or chemotherapy; with some recent clinical studies reporting the testing of these in combination with a single type of therapeutic monoclonal antibody. As also pointed out previously, the fact that Rituxan® is the first antibody to be approved for treatment of any B cell malignancy attests to the unpredictabilities associated with use of antibodies for therapy, and especially treatment of B cell malignancies. To Applicants' knowledge, the present invention would constitute the first known therapeutic treatment of a leukemia using two different antibodies. Given the absence of any precedent for the claimed invention in the prior art, and given that the prior art references neither disclosed nor

suggested using the claimed combination of antibodies to treat leukemia, there is no basis for the position that one of ordinary skill in the art would have been motivated by the teachings of the cited prior art references to practice the claimed invention with a reasonable expectation of success.

The disclosed cytotoxic effects were obtained using unconjugated and non-radiolabeled anti-CD40L and anti-CD20 antibodies, and so would be obtained as a non-obvious "baseline" level of cytotoxicity when either or both of the antibodies are conjugated to a cytotoxic moiety for antibody-mediated delivery of the cytotoxic group to target leukemia cells, are radiolabeled for radioimmunotherapy, or are used in combination with an alkylating chemotherapeutic agent. Accordingly, non-obvious cytotoxic effects are obtained using antibodies that are radiolabeled or are conjugated to a cytotoxic moiety, or are used in combination with an alkylating chemotherapeutic agent to treat leukemia, just as they are obtained using unconjugated and non-radiolabeled anti-CD40L and anti-CD20 antibodies.

In view of the foregoing, the Applicants respectfully request withdrawal of the rejection of the claims as being obvious under 35 U.S.C. §103.

Regarding Provisional Rejection of the Claims for Obviousness-type Double Patenting:

Claims of the application are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of co-pending U.S. Application No. 09/772,938. The Applicants respectfully request that this rejection be held in abeyance until allowance is negotiated. At that time, if the claims in the instant application are still deemed to be obvious in view of the claims of the issued patents, Applicants will submit a terminal disclaimer to obviate this rejection.

The Applicants' affirm that a terminal disclaimer will be submitted when the claims in the instant application are found to be allowable, but for the outstanding obviousness-type double patenting rejection over claims of co-pending U.S. Application No. 09/772,938. If additional response to the provisional obviousness-type double patenting rejection is required, or if the Examiner has any further questions or issues to raise regarding the subject application, it is respectfully requested that he contact the undersigned so that such issues may be addressed expeditiously.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By: _____

Robin L. Teskin
Registration No. 35,030

Date: December 10, 2002

1600 Tysons Boulevard
McLean, Virginia 22102
(703) 905-2000
(703) 905-2500